AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method for constitutive and/or inducible gene knock down in a mouse, which comprises stably integrating by homologous recombination an expression vector into a polymerase II dependent locus of the genome of the mouse and achieving a reduction in the activity of a product of said gene, said expression vector comprising a short hairpin RNA (shRNA) construct under control of a ubiquitous promoter and homologous sequences which integrate through homologous recombination at a polymerase II dependent locus of the genome of the mouse, wherein the ubiquitous promoter is ~~selected from the group consisting of~~ a polymerase III dependent H1 promoters~~.~~

2. (Canceled)

3. (Canceled)

4. (Canceled)

5. (Previously Presented) The method of claim 1, wherein the polymerase II dependent locus is selected from the group consisting of a Rosa26, collagen, RNA polymerase, actin and HPRT locus.

6. (Previously Presented) The method of claim 1, wherein the expression vector further contains functional sequences selected from the group consisting of splice acceptor sequences, polyadenylation sites and selectable marker sequences.

7. (Canceled)

8. (Canceled)

9. (Canceled).

10. (Currently Amended) The method of claim 1, wherein the ubiquitous H1 promoter is a constitutive promoter.

11. (Currently Amended) The method of claim 1, wherein the ubiquitous promoter is an inducible H1 promoter.

12. (Previously Presented) The method of claim 11, wherein the inducible promoter is a promoter containing an operator sequence selected from the group consisting of tet, Gal4, and lac.

13. (Canceled)

14. (Canceled)

15. (Previously Presented) The method of claim 1, wherein the expression vector is a Pol III dependent promoter driven shRNA construct to be integrated into a ubiquitously active Pol II dependent locus.

16. (Currently Amended) The method of claim 15, wherein the promoter is a constitutive H1 ~~or U6~~ promoter.

17. (Currently Amended) The method of claim 15, wherein the promoter is an inducible ~~U6 or~~ H1 promoter.

18. (Canceled)

19. (Canceled)

20. (Original) The method of claim 1, wherein the shRNA comprises at least one DNA segment

A-B-C

wherein

A is a 15 to 35 bp DNA sequence with at least 95% complementarily to the gene to be knocked down;

B is a spacer DNA sequence having 5 to 9 bp forming the loop of the expressed RNA hair pin molecule, and

C is a 15 to 35 bp DNA sequence with at least 85% complementarily to the sequence A.

21. (Original) The method of claim 20, wherein A is a 19 to 29 bp DNA sequence.

22. (Previously Presented) The method of claim 20, wherein the DNA sequence A is 100% complementary to the gene to be knocked down.

23. (Original) The method of claim 20, wherein C is a 19 to 29 bp DNA sequence.

24. (Previously Presented) The method of claim 1, wherein the shRNA comprises a stop and/or polyadenylation sequence.

25. (Canceled)

26. (Previously Presented) The method of claim 1, wherein the method for constitutive and/or inducible gene knock down in a mouse comprises integrating the expression vector into ES cells of the mouse.

27. (Currently Amended) A mouse having stably integrated by homologous recombination at a polymerase II dependent locus of the mouse an expression vector comprising a short hairpin RNA (shRNA) construct under control of a ubiquitous promoter and homologous sequences which integrate at a polymerase II dependent locus of the genome of the mouse, wherein the ubiquitous promoter is ~~selected from the group consisting of~~a polymerase III dependent H1 promoters, said mouse, as a result of expression of said shRNA, exhibiting a reduction in the activity of a product of one of its genes targeted by said shRNA compared to a mouse of the same species that does not express said shRNA.

28. (Canceled)

29. (Canceled)

30. (Currently Amended) An expression vector comprising a short hairpin RNA (shRNA) construct under control of a ubiquitous promoter and homologous sequences which integrate at a polymerase II dependent locus of the genome of a mouse, wherein the ubiquitous promoter is ~~selected from the group consisting of~~a polymerase III dependent H1 promoters~~.~~

31. (Currently Amended) ~~An~~ The expression vector ~~for constitutive and/or inducible gene knockdown in a mouse~~of claim 30, wherein said expression vector when introduced into a mouse stably integrates at the *rosa26* locus in the genome of said mouse, and wherein said expression vector comprises:

a) a ubiquitous H1 promoter ~~selected from the group consisting of a snRNA promoter, a RNAse P RNA promoter, a Trna promoter, a 7SL RNA promoter, and a 5 S Rrna promoter~~;

b) a short hairpin RNA (shRNA) sequence under the control of said ubiquitous promoter, wherein said shRNA sequence comprises at least one DNA segment

A-B-C

wherein

A is a 15 to 35 bp DNA sequence with at least 95% complementarily to the gene to be knocked down;

B is a spacer DNA sequence having 5 to 9 bp forming the loop of the expressed RNA hair pin molecule, and

C is a 15 to 35 bp DNA sequence with at least 85% complementarily to the sequence A;

c) a splice acceptor sequence under the control of the endogenous *rosa26* promoter; and

d) a stop and/or polyadenylation sequence.

32. (Previously Presented) The expression vector of claim 31, wherein A is a 19 to 29 bp DNA sequence.

33. (Previously Presented) The expression vector of claim 31, wherein the DNA sequence A has 100% complementarily to the gene to be knocked down.

34. (Previously Presented) The expression vector of claim 31, wherein C is a 19 to 29 bp DNA sequence.

35. (Previously Presented) The expression vector of claim 31, wherein the shRNA sequence is selected from the group consisting of SEQ ID NOS.: 19-220.

36. (Currently Amended) The expression vector according to claim 31, which comprises:

a) a ~~U6 or~~ H1 promoter;

b) shRluc or shFluc under the control of said promoter;

c) an adenovirus splice acceptor sequence; and

d) a polyadenylation sequence.

37. (Previously Presented) A method for gene knock down in a mouse, said method comprising:

a) providing an expression vector according to claim 31;

b) stably integrating said expression vector into the *rosa26* locus of the genome of embryonic stem cells of said mouse by homologous recombination; and thereby

c) achieving an at least 30% reduction in the activity of an expression product of said gene.

38. (Previously Presented) A mouse having an expression vector according to claim 31 stably integrated into the *rosa26* locus of the genome of cells of said mouse by homologous recombination, said mouse, as a result of expression of the shRNA contained in said expression vector, exhibiting a reduction in the activity of a product of one of its

genes targeted by said shRNA compared to a mouse of the same species that does not express said shRNA.